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New Therapeutic Options for the Treatment of Kpc (Klebsiella Pneumoniae Producing Carbapenemase)

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Abstract: Background: Klebsiella pneumoniae producing carbapenemase (KPC) cause serious infections in debilitated and immunocompromised patients, is associated with prolonged hospital stay and increased mortality rates (25-70%). Furthermore, some KPCs have started showing discrepancy between genotype and phenotype, with limited therapeutic options (colistin and tigecycline are not always effective).

Daptomycin (DAP) is a cyclic anionic lipopeptide used against S. aureus infections. The mechanism of action of DAP involves a functional disruption of the cytoplasmic membrane causing depolarization and cell death. Methods: Clinical KPC strains were obtained from diverse clinical sources; susceptibility testing to DAP was performed by E-test and to meropenem (MER) and minocycline (MIN) by disk diffusion, broth dilution and BMD. Carbapenemase were determined by the Hodge Test and by genetic methods (PCR). Bactericidal synergy assays for DAP, MER, MIN were performed using MH broth +50 µg/mL Ca²⁺ for DAP. In vitro synergy-kill experiments were performed with 10 µg/ml DAP, 6 µg/ml MER and 20 µg/ml MIN. Treatment of infected G. mellonella larvae (10/group) was performed with DAP, MER or MIN alone or in combination. Larvae were inoculated with the corresponding live KPCs strains (1.5 × 10⁶ CFU) infected, treated at 2 h post-inoculation (designated 0 h) 24 and 48 hs with doses of DAP (10mg/kg), MER (10mg/kg), MIN (4mg/ml). Worms were monitored daily, and recorded for any deaths for a total of 14 days. Results: Drugs alone did not show bactericidal effects.

In contrast, when administered together, the combination of DAP/MER was synergistic as demonstrated by cell killing at 24 h ≥ 4 log CFU while MER/MIN exhibit ≥ 3 log CFU vs. single agents and the initial inoculum. In-vivo model, groups of KPC-injected worms untreated (PBS) or single-drug treated displayed very low survival rates (≤ 20 -10%, days 11-14), the DAP/MER and MER/MIN combination resulted in survival rates between 90-80% at days 8-9. Uninfected worms treated with PBS showed 100/90% survival. Conclusions: These results suggested that DAP/MER and MER/MIN combinations may have a major impact as an anti-infective alternative.